REDUCING IMMUNOGENICITIES OF IMMUNOGLOBULINS BY FRAMEWORK-PATCHING

ABSTRACT OF THE INVENTION

A novel approach named framework (FR)-patching, to re-engineer immunoglobulin so as to reduce the potential immunogenicity, when used in the intended species, in particular, humans, without significant alterations in the specificity and affinity of the resultant immunoglobuin is described. The method differs from previously reported approaches of chimerization, CDR-grafting and/or humanization in that, the variable region sequence of the immunoglobulin to be re-engineered is compartmentalized into FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4, according to the Kabat's method, or any other conventional classification, and each individual FR sequence is dealt with separately and independently, and replaced by the corresponding FR selected from a particular host species, for example human, without modifying the CDR sequences, using a set of criteria described in this invention. The method provides flexibility in the choice of framework sequences, increasing the chances of success in maintaining the original specificity and affinity after the re-engineering. Most importantly, it minimizes the need to introduce framework amino acids derived from the parent immunoglobulin, thereby reducing the chances of creating new T- and B- cell epitopes in the resultant immunoglobulin. Both heavy and light chain immunoglobulins can be modified according to this invention, and when both chains are combined to form an intact antibody, the re-engineered, or framework-patched, or FR-patched immunoglobulins of the present invention will be substantially non-immunogenic when used in the intended species, for example, human, with substantial retention of the specificity and affinity of the parent immunoglobulin to the antigen, which can be tumor-associated, or tumor-specific proteins, or chemical haptens, or any other compounds, structures, or entities with an epitope for interaction.